

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/012953

International filing date (day/month/year)
16.11.2004

Priority date (day/month/year)
21.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07D277/20, C07D417/06, A61K31/426, A61K31/427, A61P37/06

Applicant
ACTELION PHARMACEUTICALS LTD

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/012953

1AP20 Rec'd PCT/PTO 19 MAY 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. II Priority

1. ☐ The following document has not been furnished:

☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 7-17 and 37-39

because:

- ☒ the said international application, or the said claims Nos. 7-17 and 37-39 for industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-46
	No: Claims	1
Inventive step (IS)	Yes: Claims	2-46
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-6,18-36,40-46
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/012953

IAP20 Rec'd PCT/PTO 19 MAY 2006

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 7-17 and 37-39 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.

Reference is made to the following documents:

- D1: MA, TONGHUI ET AL: JOURNAL OF BIOLOGICAL CHEMISTRY , 277(40), 37235-37241, 2002, XP002276764
- D2: JANUSZ J M ET AL, JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, 1998, pages 3515-3529, XP002223203
- D3: EP-A-1 219 612 (SHIONOGI & CO., LTD) 3 July 2002
- D4: WO 96/20936 A (SUNKYONG INDUSTRIES CO., LTD) 11 July 1996
- D5: CARTER, PERCY H. ET AL.; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA , 98(21), 11879-11884, 2001, XP002316430

The present application is related to 5-benzylidene-2-imino-thiazolidin-4-one compounds of formula (I) and the pharmaceutical compositions containing these compounds.

D1 discloses in Figure 3, p.37238 the compound CFTR_{act}-04, which is a specific compound falling under the scope of claim 1.

Thus, the subject-matter of claim 1 is not novel over D1.

D2 describes COX and 5-LOX inhibitors useful as antiinflammatory and analgesic agents (see in particular, compound 53, scheme 5, p.3519). This compound differs from those claimed because both nitrogen atom (the one of the thiazolidinone ring and the imino group) are unsubstituted.

D3 discloses immunosuppressants agents that are characterised by a 2-phenylimino-thiazolidine ring (see I-110 to I-112 in Table 6, p.26).

The compounds of D4, useful for the treatment of disorders mediated by platelet-activating factor and/or leukotrienes, differ from those claimed because they miss the 2-imino

substituent of the thiazolidin-4-one ring (see e.g. EX 120-125, Table 2, p.44).

The TNF- α ligands of D5 useful for treating TNF-based autoimmune conditions differ from the claimed compounds because these compounds have a 2-thioxo group instead of a 2-imino group and have a substituted furanyl ring instead of the para-substituted phenyl ring. Thus, the subject-matter of the present application is novel over D2-D5.

2.

For potentially novel subject-matter the following points would have to be noted in the view of inventive step (**Art. 33(1) and 33(3) PCT**):

The present application is related to 5-benzylidene-2-imino-thiazolidin-4-ones of formula (I) and (II), the pharmaceutical compositions containing these compounds and their use as immunosuppressants for the prevention or treatment of disorders associated with an activated immune system such as organ transplant rejection or autoimmune syndromes. D3 is considered to be the closest prior art since it discloses 2-imino-1,3-thiazines and 2-imino-1,3-thiazolidines as immunosuppressants.

D5 discloses also thiazolidin-4-ones that are TNF- α inhibitors useful for the treatment of human autoimmune diseases. In Table 1 of D5 the comparison between 2-thioxo-thiazolidin-4-one and 2-imino-thiazolidin-4-one is done (see entry 3 and entries 6 and 7): it is shown and also stated on p. 11881, 2nd column in D5 that "the replacement of the sulfur atom of the rhodanine thiocarbonyl with either oxygen or nitrogen abrogated the binding activity of the compounds".

Thus, by combining D3 with D5, the skilled person would be led to add a 4-oxo group on the thiazolidine ring of the compounds of D3 but there is no indication that would suggest him to add a para-substituted-benzylidene in the 5-position of the thiazolidine ring of the compounds of D3.

Due to the structural differences re the active compounds in D3 (the missing 5-benzylidene substituent and the missing 4-oxo group on the thiazolidine ring) it cannot be said with any degree of accuracy that the skilled person, faced with the problem of providing further novel immunosuppressant agents, would have been unambiguously led to prepare the compounds of the present application-even by combination of D3 with D5.

Thus, an inventive step, based on the unexpected ability of the claimed compounds to act as immunosuppressants (as shown by the pharmacological results given on Table 1, p.3 in the application) can be acknowledged (Article 33(1) and 33(3) PCT).

3.

For the assessment of the present claims 7-17 and 37-39 on the question whether they are

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International application No.

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industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
US2004/167192	26-08-2004	16-01-2004	
WO2004/007491	22-01-2004	10-07-2004	10-07-2002

These documents are related to 5-benzylidene-2-imino-thiazolidin-4-ones as immunosuppressant agents.

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